

REMARKS

The Office Action dated April 1, 2010, has been received and carefully noted. The following remarks are being submitted as a full and complete response thereto.

Initially, Applicants thank the Examiner for not making this Office Action final, in view of the citation of new references.

Claims 1-26 and 28-31 are pending in this application, with claims 1, 23, and 29-31 being independent. By this Amendment, claims 29-31 have been amended. Applicants submit that no new matter has been presented herein.

Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 29-31 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The reasons for this rejection are set forth on pages 2-3 of the Office Action.

Applicants have amended claims 29-31 to address the bases for this rejection. In view of the amendments set forth above, Applicants respectfully request withdrawal of the rejection of claims 29-31 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 103(a)

Claims 1-11, 13-16, and 18-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Timmins (U.S. Patent No. 6,031,004) and Balkan (U.S. Patent Publication No. 2003/0139434) as evidenced by Tyler (W.S. Tyler Canada, product and

price catalog), Martin (U.S. Patent No. 6,110,497) and Shimizu (U.S. Patent No. 6,328,994). Applicants respectfully traverse this rejection.

Timmins is cited for allegedly disclosing salts of the anti-diabetic agent metformin, including metformin fumarate and metformin succinate, which may be employed alone or in combination with another anti-hyperglycemic agent (see Abstract). Timmins discloses that the dosage form may be a tablet or capsule, among others (see column 4, lines 49-52). Timmins further discloses that the dosage forms may include from about 1% to about 80% excipients, such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, calcium carbonate, and microcrystalline cellulose (see column 5, lines 8-12); one or more binders such as polyvinylpyrrolidone (having a molecular weight of preferably about 40,000), lactose, starches and polyethylene, among others (see column 5, lines 15-23); about 2% to about 8% by weight of disintegrants, such as croscarmellose sodium, crospovidone/cross-linked polyvinyl pyrrolidone, sodium starch glycolate, corn starch and microcrystalline cellulose (see column 5, lines 24-30); other excipients such as preservatives, silicon dioxide, and polymeric celluloses (see column 5, lines 34-46); and the sweetening agent xylitol, and the flavoring agents grape flavor, spice flavor and raspberry flavor (see column 10, lines 1-35).

In Example 4, Timmins discloses a tablet formulation containing the active agent metformin succinate in an amount of 80% (600/748x100), the binder hydroxypropylmethyl cellulose in an amount of 2% (15/748x100), the disintegrant croscarmellose sodium in an amount of 6% (45/748x100), the filler/diluting agent microcrystalline cellulose in an amount of 10% (80/748x100), and the additional

excipient magnesium stearate. Timmins further discloses that the formulation of Example 4 is prepared by wet granulation, and includes the steps of mixing, granulating, drying and compressing into tablets (see column 7, lines 45-60).

Timmins also discloses that additional active ingredients may be included, such as pioglitazone (see column 3, line 64), thiazolidinedione/glitazone (see column 4, line 2), glimepride, glipryride, glipizide, chlorpropamide, glicazide and acarbose (see column 4, lines 24-26).

Regarding the size of the granules, the Office Action indicates that Timmins discloses that the mixtures of ingredients are passed through a #12 to #40 mesh screen (6:3), which according to Tyler indicates a size of from 425 microns to 1.7 mm (see Tyler, page 3, table columns 1-2). However, this statement is inaccurate, for reasons that Applicants will discuss below.

The Office Action admits that Timmins does not disclose compositions that include a dipeptidyl peptidase inhibitor and/or a sugar coating. However, Balkan is cited for allegedly disclosing these features.

Balkan is cited for disclosing combination pharmaceutical compositions which include dipeptidyl peptidase four (DPP-IV) inhibitors and at least one anti-diabetic compound (see Abstract). Balkan further discloses compositions containing the anti-diabetic compound metformin, among others (see [0150]). Balkan further discloses the combination comprising DPP728 plus metformin (see [0175]). Balkan further discloses pharmaceutical preparations that are prepared by conventional mixing, granulating, and sugar-coating (see [0190]). Balkan further discloses that, if desired, the mixture may be processed to form granules, tablets, or sugar-coated tablet cores (see [0190]).

Shimizu is cited for allegedly disclosing orally disintegrating tablets comprising a coating layer and a core, where the core is 75-85% of the tablet weight (see col. 15, lines 20-40). Martin is cited for allegedly disclosing a dispersible tablet formulation composed of granulate particles and extragranular excipients, where the granulate particles may comprise 70-95% of the total tablet weight (see col. 2, lines 35-38).

The Office Action takes the position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine a DPP-IV inhibitor with a metformin pharmaceutical composition, as suggested by Balkan, because Timmins suggests the use of metformin in combination with other anti-diabetic drugs, and because Balkan discloses that DPP-IV inhibitors are anti-diabetic drugs suitable for use with metformin. The Office Action asserts that one of ordinary skill in the art would have been motivated to combine Balkan with Timmins because the resulting formulation would have increased efficacy due to the combination of the two anti-diabetic drugs. The Office Action also asserts that it would also have been obvious to produce a sweetener-coated formulation because the sweetener would have a more appealing taste for the user, and would therefore increase patient compliance. The Office Action further asserts that one skilled in the art would have had a reasonable expectation of success in producing the presently-claimed invention.

Applicants respectfully disagree with the positions taken in the Office Action.

The presently-claimed invention was developed in order to address the problem of preparing oral dosage forms containing metformin, which is difficult to work with because of its low compressibility, and low binding capability. These issues result in dosage forms that have an unacceptably large size. Further, even when the issue of

the size of the dosage form is overcome, there are still problems associated with the trade-offs between providing acceptable mechanical properties to the dosage form and preserving its physical integrity during storage, and the ability of such dosage forms to dissolve quickly on contact with an aqueous solution. Attempts to solve this problem by providing liquid dosage forms have not been acceptable due to their lower stability.

The presently-claimed invention solves these problems preparing oral dosage forms containing metformin by providing solid dosage forms comprising particles having a size that is less than 710 microns. According to certain embodiments of the invention, when the particles that make up the oral dosage forms are dispersed in water, the dispersion is homogenous, and no particle resulting from the disintegration of the dosage form has a size larger than 710 microns, as determined by passing the dispersion through a sieve having a nominal mesh size of 710 microns. See page 5. According to further embodiments, the particles that result from the disintegration of the dosage form include an internal core comprising the active ingredient and appropriate excipients, and an external layer comprising a sweetening agent and appropriate excipients. See page 11. As demonstrated by the data contained in Tables 11 and 12 of the specification, the presently-claimed dosage forms beneficially provide a pharmacokinetic profile that is equivalent to Glucophage®-brand metformin tablets, without any of the drawbacks described above.

Applicants submit that Timmins relates to dosage forms containing dibasic acid salts of metformin as an alternative to metformin hydrochloride, which is said to have an unpleasant taste and is considered problematic from a manufacturing standpoint. The alternative salts have improved taste and handling properties, and are “significantly less

soluble in water than the hydrochloride salt and thus provide the opportunity for formulating metformin in controlled release systems.” See col. 2, lines 38-43. Timmins fails to disclose or suggest the preparation of dispersible or orodispersible dosage forms, as claimed and as defined at page 4 of the present specification. Timmins provides no disclosure to enable one skilled in the art to prepare such a dosage form.

Timmins discloses at column 6, lines 2-3, that the medicament(s) and optional fillers are mixed and passed through a #12 to #40 mesh screen (425 microns to 1.7 mm), followed by adding optional filler/binder, a disintegrant, and a lubricant, and then mixing and compressing the mixture. The Office Action again takes the position that this disclosure renders the size feature of the presently-claimed invention obvious, but Applicants respectfully disagree. Applicants submit that although the active ingredient is sieved in Timmins, the steps of adding additional excipients to the sieved active ingredient, followed by mixing and compressing, will result in a mixture containing particles that are larger than 710 microns.

Applicants submit the presently-claimed invention specifically relates to pharmaceutical compositions comprising particles containing a metformin active ingredient and having a size that is less than 710 microns, where the particles comprise the various components set forth in the claims. Further, according to some embodiments, the metformin used in the presently-claimed invention preferably has a grain size of less than 100 microns, which is far smaller than the grain size for the active ingredients disclosed in Timmins. See page 8 of the present specification.

Balkan fails to remedy these deficiencies of Timmins with respect to the presently-claimed invention, because although it discloses combinations of DDP-IV

inhibitors and an antidiabetic compound such as metformin, it utterly fails to disclose or suggest dispersible or orodispersible pharmaceutical compositions, or dosage forms that include particles having a size that is less than 710 microns.

Shimizu relates to an orally disintegratable tablet containing granules of the active agent lansoprazole, where the granules are less than 400 μm in size, including a coating of an enteric coating agent and a sustained-release agent. Martin relates to a tablet formulation for a beta-lactam antibiotic optionally combined with a beta-lactamase inhibitor, where the tablet is made by compacting a granulate that is from 100 μm to 2 mm in diameter. Shimizu and Martin are merely cited for disclosing the amount of the core relative to the tablet weight, and do not remedy the deficiencies of Timmins and Balkan. Further, Applicants submit that one skilled in the art attempting to prepare a dispersible or orodispersible formulation containing metformin would not look to the disclosures of Shimizu and Martin. Shimizu and Martin relate to disintegratable dosage forms of active agents that are unrelated to metformin, and do not address the unique problems encountered when preparing formulations containing metformin.

Further to the comments set forth above, Applicants also offer the following comments regarding the "Response to Arguments" section.

The Office Action took the position that the preamble statement "dispersible or orodispersible solid pharmaceutical formulation" is regarded as an intended use statement, and that so long as the prior art is capable of performing the intended use it is deemed to meet this requirement of the claim. In response, Applicants submit that the use of the phrase "dispersible or orodispersible" in the presently-claimed invention is not properly interpreted as a mere intended use statement; rather, it describes a

structural feature of the presently-claimed pharmaceutical compositions that is necessary to understand the invention and how it distinguishes over the prior art discussed in the specification (i.e., conventional tablets containing metformin, including those described on pages 2-3 of the specification). See, e.g., *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257, 9 U.S.P.Q.2. 1962, 1966 (Fed. Cir. 1989) (The determination of whether preamble recitations are structural limitations can be resolved only on review of the entirety of the application "to gain an understanding of what the inventors actually invented and intended to encompass by the claim."). Applicants have previously argued (and argue again here) that the claims require that the pharmaceutical compositions are orodispersible or dispersible. See *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808-09, 62 U.S.P.Q.2d 1781, 1785 (Fed. Cir. 2002) ("[C]lear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention.).

In response to Applicants' arguments that the sieved particles of Timmins, which are mixed and compressed with additional ingredients, are larger than 710 μm , the Office Action took the position that "the process is not contrary to the process of the instantly claimed invention." (Emphasis in original.) Timmins discloses the use of wet granulation, including mixing, granulating, drying, and compressing into tablets. The fact that this process is "not contrary" to one of the processes that may be used to make the pharmaceutical compositions of the present invention (which are not limited to any particular method of manufacture) does not alter the fact that the process used in

Timmins results in formation of particles that are larger than 710 μm . Regardless of how they are made, the particles of Timmins do not meet the requirements of the presently-claimed invention.

The Office Action further indicated that the broadest reasonable interpretation of “particles with a size lower than 710 μm ” includes tablets composed of particles with sizes lower than 710 μm , and that the term “particle” includes atoms and molecules of the dosage form. Applicants assume that this statement is intended to mean that the Office Action is interpreting Timmins in a manner such that it discloses the feature “particles with a size lower than 710 μm ” because the dosage forms of Timmins (and indeed all forms of matter) are made up of atoms and molecules, which are smaller than 710 μm . Applicants submit that this interpretation of “particles with a size lower than 710 μm ” ignores the language of the claims, and instead relies on an overly broad dictionary definition that is being used to effectively read this feature out of the claims.

In this case, the claims are quite clear that the “particles” are smaller than 710 μm , and that the “particles” comprise at least metformin active ingredient (optionally in the form of a salt), binding agent, disintegrating agent, diluting agent, sweetening agent, and one or more additional excipients. Applicants have amended instances in which the word “granule” was used in place of “particle” in claims 29-31 in order to remove any ambiguity. Applicants’ claims specifically and unambiguously exclude the interpretation of the size feature advanced in the Office Action that is being used to maintain the rejections, and therefore Applicants submit that the rejection must be withdrawn.

Accordingly, because the combination of Timmins and Balkan fails to disclose or suggest all of the features of the presently-claimed invention, and the deficiencies are

not remedied by further combination with Tyler, Shimizu, and Martin, no *prima facie* case of obviousness has been established.

In view of the amendments and remarks presented above, Applicants submit that claims 1-11, 13-16, and 18-28 are not unpatentable over any combination of Timmins, Balkan, Tyler, Shimizu, and Martin, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claim 12 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Timmins and Balkan, as evidenced by Tyler, as applied to claims 1-11, 13-16, and 18-28 above, and further in view of Bonhomme (U.S. Patent No. 6,372,790). Applicants respectfully traverse this rejection.

The deficiencies of the combination of Timmins, Balkan, and Tyler are discussed above.

Bonhomme is cited for allegedly disclosing a dosage form containing metformin combined with a fibrate selected from fenofibrate and bezafibrate.

Applicants submit that Bonnhome fails to remedy the deficiencies of the combination of Timmins, Balkan, and Tyler.

In view of the amendments and remarks presented above, Applicants submit that claim 12 is not unpatentable over any combination of Timmins, Balkan, Tyler, and Bonhomme, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claim 29 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Timmins and Balkan, as evidenced by Tyler, as applied to claims 1-11, 13-16, and 18-28 above, and further in view of Ohno (U.S. Patent No. 4,017,598), and further evidenced by Bennett ("Pharmaceutical Production: An engineering guide," 2003, Institution of Chemical Engineers, Chapter 6, pp. 111-153). Applicants respectfully traverse this rejection.

The deficiencies of the combination of Timmins, Balkan, and Tyler are discussed above.

Ohno is cited for allegedly disclosing adding a sweetener as an extragranular excipient before the final step of tablet compression.

Bennett is cited for allegedly disclosing the knowledge of a person having ordinary skill in the art of pharmaceutical formulation at the time the presently-claimed invention was made.

Applicants submit that Ohno and Bennett fail to remedy the deficiencies of the combination of Timmins, Balkan, and Tyler.

In view of the amendments and remarks presented above, Applicants submit that claim 29 is not unpatentable over any combination of Timmins, Balkan, Tyler, Ohno, and Bennett, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 30 and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Timmins and Balkan as evidenced by Tyler as applied to claims 1-11, 13-16, and

18-28 above, and further in view of Venkatesh (U.S. Patent No. 6,475,510), and further evidenced by Bennett. Applicants respectfully traverse this rejection.

The deficiencies of the combination of Timmins, Balkan, and Tyler are discussed above.

Venkatesh is cited for allegedly disclosing dry granulation, as well as adding a sweetener as an extragranular excipient before the final step of tablet compression.

Bennett is cited for allegedly disclosing the knowledge of a person having ordinary skill in the art of pharmaceutical formulation at the time the presently-claimed invention was made.

Applicants submit that Venkatesh and Bennett fail to remedy the deficiencies of the combination of Timmins, Balkan, and Tyler.

In view of the amendments and remarks presented above, Applicants submit that claims 30-31 are not unpatentable over any combination of Timmins, Balkan, Tyler, Venkatesh, and Bennett, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

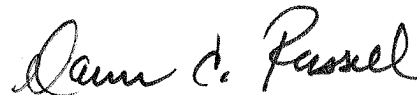
CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration of the application, withdrawal of the outstanding rejections, allowance of Claims 1-26 and 28-31, and the prompt issuance of a Notice of Allowability.

Should the Examiner believe anything further is desirable in order to place this application in better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

In the event this paper is not considered to be timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to counsel's Deposit Account No. 01-2300, referencing attorney docket number 030363.00003.

Respectfully submitted,



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